Clinical Pharmacology & Toxicology Pearl of the Week

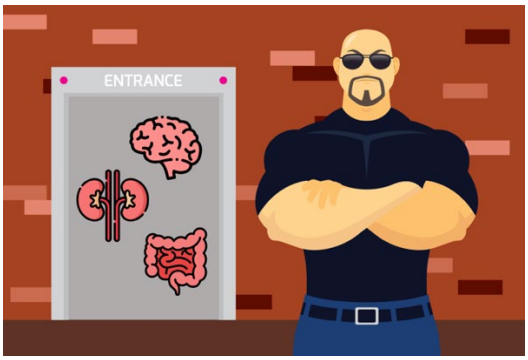
~ P-glycoproteins ~

Case

- ✓ A 56-year-old female presents to the emergency department with a 4-day history of nausea, vomiting, diarrhea and general weakness. Her past medical history includes atrial fibrillation, hypertension, and dyslipidemia. Her home medications include apixaban, diltiazem, and atorvastatin. She started colchicine for gout 5 days ago.
- ✓ Her bloodwork is notable for a pancytopenia (Hb 82, WBC 1.5, and platelets 95).
- ✓ Clinical Question: If she was taking colchicine at therapeutic dosing, are there any drug interactions that could increase the risk of colchicine toxicity?

Background

- ✓ Permeability-glycoproteins (Pgps) are an important group of efflux protein transporters on cell membranes that act to pump drugs outside out cells. A good analogy is to think of Pgps like the bouncers that prevent drugs from entering cells.
- ✓ These Pgps are found in various tissues with excretory functions, including the gastrointestinal tract, blood-tissue barriers (blood-brain barrier, blood-testis barrier, placenta), the liver and the kidneys.



Effect on Pharmacokinetics

- ✓ *Absorption*
  - Pgps are found in the apical (luminal) membrane of the intestines which act to decrease drug absorption.
  - Inhibition of Pgp can result in increased bioavailability, while induction of Pgp reduces bioavailability.
- ✓ *Distribution*
  - Once a drug has reached systemic circulation, Pgps further limit drug penetration into several sensitive tissues, including the brain.
  - Pgp inhibitors can increase the uptake of drug from the blood circulation to the brain, while inducers decrease uptake to the brain.
- ✓ *Elimination*
  - Pgps are expressed on the luminal membrane of renal proximal tubule cells, and act to pump drugs into the urine to be excreted. They are also found in the liver, which similarly pump drugs into the bile.

Drug Interactions

- ✓ Several drugs can act as substrates, inhibitors, or inducers of Pgp.
- ✓ There are many overlapping inhibitors and inducers between cytochrome CYP3A4 and Pgps, with many drug interactions involving both systems.

P-glycoprotein inducers	P-glycoprotein inhibitors	P-glycoprotein substrates
– Phenobarbital – Phenytoin – Carbamazepine – Rifampin – St. John's Wort	– Clarithromycin/Erythromycin – Ketonazole/Itraconazole – Amiodarone – Verapamil – Diltiazem – Quinidine – Bisoprolol/Carvedilol – Nicardipine – Protease inhibitors – Sirolimus/Tacrolimus – Atorvastatin/Simvastatin – Cyclosporine – Tamoxifen – Grapefruit juice	– Colchicine – Digoxin – Loperamide – Dabigatran

Case Resolution:

- ✓ Colchicine is a Pgp substrate. The patient's home medications included verapamil and atorvastatin, both of which are known to be Pgp inhibitors. This likely resulted in colchicine toxicity, as manifested by her gastrointestinal symptoms and pancytopenia.
- ✓ The colchicine was discontinued, and the patient was admitted to hospital for monitoring with daily CBCs. In consultation with hematology, she was administered granulocyte colony-stimulating factor which gradually improved her cell lines, without any signs of developing secondary infection.
- ✓ An awareness of potential transporter-related drug-drug interactions is important and should be carefully assessed when prescribing any of the high-risk medications above.

References

1. Nelson L, Lewin N, Howland M, Hoffman R, Goldfrank L, Flomenbaum N. Goldfrank's Toxicologic Emergencies. 11th ed. New York: McGraw Hill Medical; 2019

2. Lin J, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. Clin Pharmacokinet. 2003;42(1):59-98.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultations are also available through Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-1212 (SK).